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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,051	12/04/2003	Michael J. Caplan	2006517-0009	9832
24280 7590 04/16/2008 CHOATE, HALL & STEWART LLP TWO INTERNATIONAL PLACE BOSTON, MA 02110			EXAMINER HUYNH, PHUONG N	
			ART UNIT 1644	PAPER NUMBER
			NOTIFICATION DATE 04/16/2008	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No. 10/728,051	Applicant(s) CAPLAN, MICHAEL J.	
	Examiner PHUONG HUYNH	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 February 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 34-45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 34-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 29, 2008 has been entered.
2. Claims 34-44 are pending and are being acted upon in this Office Action.
3. The substitute specification filed February 29, 2008 to incorporate essential material into this application from 09/141,220 is effective and has been entered.
4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.
5. Claims 34-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (newly cited, issued March 30, 1999; PTO 892), US Pat No. 3,097,141 (newly cited, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892).

The WO 99/38978 publication teaches a pharmaceutical composition comprising *E coli* comprising at least one recombinant modified allergen such as modified peanut allergen Ara h1, Ara h2 and Ara h3 where the center of one or more amino acid present in IgE binding sites of Ara h1, Ara h2 and Ara h3 have been substituted with neutral or hydrophilic amino acid or lacks a portion of the wild-type peanut allergen such that the modified peanut allergens have reduced binding to IgE as compared to the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16,

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line 22-33, claims 1-7 of the WO 99/38978 publication, in particular). The reference wild-type Ara h3 allergen of SEQ ID NO: 6 is encoded by the reference nucleotide sequence of SEQ ID NO: 5, which is identical to the claimed SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular). The reference IgE binding sites of Ara h1, Ara h2 and Ara h3 are shown in Table 4 at page 23, Table 5 at page 24 and Table 6 at page 24, respectively. The reference wild-type Ara h1 of SEQ ID NO: 2 is encoded by the reference SEQ ID NO: 1. The reference wild-type Ara h2 of SEQ ID NO: 4 is encoded by the reference SEQ ID NO: 3. The reference further teaches a method of making modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the modified peanut allergen or portion thereof has at least one amino acid that has been deleted or substituted within the IgE binding sites such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, claims 29-in particular). The reference modified peanut allergen is encapsulated inside the dead *E coli* because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm since it must be solubilized with urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular). The reference's modified peanut allergens Ara h1, Ara h2 and Ara h3 are identical to the ones to be incorporated by reference to 09/141,220. The WO 99/38978 publication teaches the modified peanut allergen is safe and efficacious for treating peanut allergy (see page 2, lines 21, claim 36 of the publication, in particular). The advantage of having IgE binding sites converted to non-IgE binding sites by masking the site or by single amino acid substitution within the center of IgE binding would be useful for immunotherapy (see abstract, page 10, in particular).

The claimed invention differs from the teachings of the reference only in that the pharmaceutical composition wherein the modified peanut allergen is encapsulated in *E coli* and the *E coli* is dead instead of alive and the *E coli* was killed by heat.

Fenton et al teach a pharmaceutical composition comprising dead *Escherichia coli* that have been engineered to express recombinant modified ras protein bearing a Gln to Leu mutation at residue 61 and a pharmaceutical carrier such as Hanks Balance Salt solution or HBSS (see page

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1855, col. 1, Immunization with heat-killed bacteria, in particular). The reference *E coli* were heat-killed by incubation at 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular). The reference recombinant Ras protein obviously located in side the *E coli* such as inclusion bodies located within the cytoplasm given the purification of Ras protein must be disrupted with sonification (see page 1854, col. 2, Purification of Ras proteins, in particular). Fenton et al further teach antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the recombinant modified protein derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity by modulating immune response to Th1 as measured by cytokines IL-2, IFN γ secreted and granuloma formation at the vaccine site (see page 1857, col. 2, full paragraph, page 1860, col. 2, second full paragraph, in particular).

Vrtala et al teach the use of recombinant non-pathogenic *Salmonella* genetically engineered to express modified birch pollen allergen Bet vI localized to the cytoplasm of *Salmonella* and mice fed with Salmonella expressing Bet vI can develop a Bet vI allergen specific Th1 immune response (see page 293, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). However, there are a number of technical and ethical problems before such *live* allergy vaccines could be used for therapy of type I allergy in patients (see page 293, col. 2, in particular).

The '799 patent teaches the use of *E coli* as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The reference *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens (see col. 9, lines 3-40, in particular). The '799 patent teaches the antigen or allergen of interest in the *E coli* can be engineered to transport across the *E coli* cytoplasmic membrane and ended up in the periplasmic space (see col. 14, line 29-31, in particular). The bacterial cell is formulated for administered orally in enteric-coated capsules (see col. 13, line 4-6, in particular).

The '141 patent teaches a method of modifying anaphylactogens which reduces toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* by heating *E coli* from about 50 to 100 °C to reduce toxicity of the antigens (see col. 1, lines 8-65, col. 2, line 1-10, in particular). The '141 patent further teaches *E coli* can be killed by chemical treatment such as

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phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide H_2O_2 (see col. 1, line 58, in particular).

Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed bacteria by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the *E coli* that is expressed the modified peanut allergen Ara h1, Ara h2 and Ara h3 with reduced ability to bind to or cross-link IgE of the WO 99/38978 publication as an allergen carrier for induction of tolerance as taught by the '799 patent by killing the *E coli* bacteria by heating from about 50 to 100°C as taught by Fenton or the '141 patent or Lecberc et al or oxidizing agent such as Hydrogen peroxide as taught by the '141 patent to avoid any ethical issues and without the need for extensive protein purification using such bacteria for treating allergy as taught by Vrtala et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify allergen because the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein such as Ara h1, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to kill the *E coli* expressing modified food allergen because Vrtala et al teach killing the microorganism that expressed modified allergen can avoid the technical and ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in patients (see page 293, col. 2, in particular). Vrtala et al further teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification while avoiding the ethical problems of such *live* allergy vaccines (see page 293, col. 2, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to use heat killed recombinant bacteria expressing the antigen of interest because Fenton et al teach heat-killed recombinant *E coli* is

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useful as a vaccine and that the antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity, and to modulate immune response to Th1 as measured by cytokines IL-2, IFN γ secreted (see page 1857, col. 2, full paragraph, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular). The '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular). The '141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of *E coli* (see col. 1, lines 8-65, col. 2, line 1-10, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

6. Claims 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (newly cited, issued March 30, 1999; PTO 892), US Pat No. 3,0997, 141 (newly cited, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892) as applied to claims 34-43 mentioned above and further in view of WO 92/14487 (newly cited, published September 1992; PTO 892) and US Pat No 6,270,723 (of record, filed Oct 2, 1998; PTO 892), Komanapalli et al (newly cited, Appl Microbil Biotechnol 49: 766-769, 1998; PTO 892) and/or Ingram et al (newly cited, J Bacteriology 144(2): 481-488, Nov 1980; PTO 892).

The combined teachings of the WO 99/38978 publication, Fenton et al, Vrtala et al, the '799 patent, the '141 patent and Leclerc et al have been discussed supra.

The claimed invention in claim 44 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed by chemical treatment instead of heat.

The claimed invention in claim 45 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed using a chemical selected from the group consisting of bleach, ozone, and alcohols instead of heat.

The WO 92/14487 publication teaches a method of safely killing *E coli* bacteria expressing various colonization factor antigens by chemical treatment such as mild or diluted formalin-treated *E coli* for use as a whole cell vaccine (see page 7-8, page 19, line 26, in particular). The WO 92/14487 publication teaches the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as greater stability of the antigen against degradation in the intestinal milieu (see page 8, lines 7-9, in particular).

The '723 patent teaches various methods of killing *bacteria* by chemical treatment such as alcohol (see col. 1, line 21, in particular), bleach (see col. 10, line 39-40, in particular) or pressure sterilization (ozone) to inactivate bacteria such as *E coli* for pharmaceutical composition (see col. 11, lines 42-67, col. 15, line 8, in particular). The '723 patent teaches these methods can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* while oxygen gas has no effect (see page 767, col. 2, results, Fig. 1, in particular). Ozone induced lipid oxidation in *E coli* and leakage of cytoplasmic contents (see abstract, see Figs 5 & 6, in particular).

Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Ingram et al teach increasing concentrations of alcohol such as ethanol and hexanol progressively inhibits the growth of *E coli* and hexanol was a much more potent inhibitor of growth than was ethanol (see page 482, col. 2, in particular). Ingram et al teach ethanol prevented the assembly of cross-linked peptidoglycan while hexanol did not inhibit such cross-linking, see page 485, col. 2, in particular.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to kill any recombinant modified peanut allergen producing *E. coli* for a pharmaceutical composition given the highly anaphylactic nature of the peanut allergen as taught by the WO 99/38978 publication by means chemical treatment such as mild or diluted formalin-treatment as taught by the WO 92/14487 publication or diluted alcohol (see col. 1, line 21, in particular), or diluted bleach (see col. 10, line 39-40, in particular) as taught by the '723 patent or alcohol as taught by Ingram or by ozone as taught by Komanapalli et al to preserve the immunogenic property of inactivated bacteria as taught by the WO 92/14487 publication.

One having ordinary skill in the art would have been motivated to do this because the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria while at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as maintaining greater stability of the antigen against degradation in the intestinal milieu as taught by the WO 92/14487 publication (see page 8, lines 7-9, in particular). The '723 patent teaches chemical treatment such as iodine, bleach, ozone, or alcohol can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular). Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* (see page 767, col. 2, results, Fig. 1, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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8. Claims 34-45 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-36 and 38-49 of copending Application No. 10/728,323. Although the conflicting claims are not identical, they are not patentably distinct from each other because the *species* of pharmaceutical composition comprising dead *E coli* comprising at least one modified peanut allergen amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen, wherein the wild-type peanut allergen is an Ara h 1, Ara h 2 or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO:2, or SEQ ID NO:3, and wherein the modified peanut allergen is encapsulated inside such as cytoplasm or periplasm of the dead *E. coli*; and a pharmaceutically acceptable carrier, as well as modified peanut allergen is located in the cytoplasm, or periplasm of dead *E. coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of instant application anticipates the *genus* of composition comprising at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen, wherein the modified allergen is encapsulated inside the dead *E. coli*; and a pharmaceutically acceptable carrier, wherein the wild-type allergen is found in nature in foods, in peanuts, milk, eggs, seafood, nuts, dairy products, fruit, as well as modified peanut allergen is located in the cytoplasm or periplasm of the dead *E coli*, and means and mode of killing by heat, chemical treatment such as iodine, bleach, ozone or alcohol of copending application 10/728,323.

Thus the issuance of a patent to instant application (*species*) anticipates the claims of the copending application (*genus*). The issuance of a patent to copending application 10/728,323 would include the claims of instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. No claim is allowed.
10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner

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can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Primary Examiner, Art Unit 1644

April 14, 2008